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A MATHEMATICAL MODEL FOR ESTIMATION OF PLUTONIUM IN THE HUMAN BODY FROM URINE DATA INFLUENCED BY DTPA THERAPY

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ABSTRACT

An empirical urinary excretion model was derived from two puncture wound cases and several inhalation cases treated with DTPA. Important excretion mechanisms for chelated plutonium and the chemistry of plutonium under physiological conditions are related to the derivation of mathematical models for single and multiple DTPA treatments. These models are used as a basis for assessing plutonium body burdens after DTPA therapy, determining the optimal DTPA dosage regimen, and evaluating the effectiveness of DTPA therapy. DTPA therapy initiated immediately after a contamination incident will reduce a body burden by a factor of about 3. A larger fraction of plutonium loosely deposited in body tissues can be removed by prolonged therapy.

An inhalation incident involving 6 workers in a ^{238}Pu oxide production facility is discussed. Worker bioassay data are compared with urinary excretion rates predicted by the Pu-DTPA model.

INTRODUCTION

Severity of an accidental intake of plutonium into the body must be determined as soon as possible to provide a basis for therapeutic treatment and exposure control. Techniques for estimating plutonium body burdens from urinalyses data not biased by a chelating agent have been available for many years. Computer programs (La62, Sn64, Be72) have been written and systemic models established to relate urinary excretion data to the body burden. DTPA therapy increases the urinary excretion rate significantly for periods longer than one hundred days (Hei69, Je72); therefore, a single DTPA treatment will limit the use of the systemic models to relate urine data and body content for several months.

The therapeutic effectiveness of DTPA to eliminate plutonium from the body is greatly reduced with delayed treatment (Ne71). Thus, prompt decisions are needed to obtain the greatest benefit from therapy. If a plutonium contamination incident occurs, the recommendation for chelation treatment must be based on available exposure data for the case in conjunction with experience gained from similar inhalation or puncture wound cases (Hei69).

Two puncture wound cases (Ve66, Jo72) and several inhalation cases treated with DTPA provided the basis for a proposed systemic model for Pu-DTPA. Mathematical expressions were derived from an empirical urinary excretion model developed from bioassay data for workers who received DTPA treatments. These expressions include functions that relate the fraction of the systemic plutonium available for chelation with the time of the initial deposition and the interval between successive treatments. Based on human Pu-DTPA excretion data these empirical expressions can be used to provide (1) an early assessment of systemic burdens for cases treated with DTPA, (2) a baseline estimate of the excretion rate from the initial systemic burden for application of a

lung model to evaluate the systemic burden resulting from a lung burden of PuO_2, (3) a basis for determining the optimal DTPA dosage schedule and (4) a means for evaluating the effectiveness of DTPA therapy.

The Pu-DTPA systemic model may be used to evaluate bioassay data for workers involved in plutonium contamination incidents. Examples are presented to show how the model is used to evaluate a worker's urinary excretion data.

PLUTONIUM ELIMINATION

Quantitative determinations of plutonium in excreta of workers are used to estimate depositions in the body and evaluate dose commitment or organ doses. The relationship between body burden and excretion rates, as a function of time after exposure, must be known to interpret excretion data. Initially urinalysis data of laboratory workers were evaluated by extrapolating tracer data from rodents to man. Based on an earlier study (Ha47) in which plutonium was deposited in the bones of rats with a toxicity similar to radium, several hospitalized persons were injected with tracer amounts of plutonium to establish the human urinary excretion rate (Ni45). Langham used the experimental data from these human subjects to develop a systemic model which describes the rate of urinary excretion for plutonium following an acute exposure (La56). This model was based on the assumption that bone is the critical organ and that regardless of the mode of exposure, plutonium would be rapidly translocated to the skeleton.

SYSTEMIC MODEL

Langham derived a power function expression to estimate human urinary excretion over a 5-year period.

$$E_u(t) = I_o A t^{-0.74} \qquad (1)$$

where $E_u(t)$ is the predicted daily excretion rate during the day (t) after an intake, I_o is the plutonium initially deposited, and A is the fraction excreted in urine during the first day (0.002). Equation (1) is somewhat awkward to use in a general analysis because it represents daily average excretion rates (rather than instantaneous) and is based on a time scale beginning at 1 day (rather than 0) and proceeding in discrete increments (rather than being continuous). It is more convenient to employ a more general expression of the same form,

$$E_u(t) = I_o A_o G(t) \tag{2}$$

in which A_o represents the excretion rate immediately after intake and G(t) represents the relative rate change.

For example, if one chooses to use Durbin's formulation (Du72), C(t) becomes

$$\left(\sum_{j=1}^{5} A_j e^{-\lambda_j t}\right) \Big/ \left(\sum_{j=1}^{5} A_j\right),$$

and

$$A_o = \sum_{j=1}^{5} A_j,$$

with $A_o = 0.0055$, $A_1 = 0.0041$, $A_2 = 0.0012$, $A_3 = 0.00013$, $A_4 = 0.00003$, $A_5 = 0.000012$ and $\lambda_1 = 0.578d^{-1}$, $\lambda_2 = 0.126d^{-1}$, $\lambda_3 = 0.0165d^{-1}$, $\lambda_4 = 0.00231d^{-1}$, and $\lambda_5 = 0.000173d^{-1}$.

The total amount excreted in urine through the m^{th} day after intake can be expressed as a sum using Langham's formulation [equation (1)];

$$I_u = I_o A \sum_{K=1}^{m} K^{-0.74} \tag{3}$$

Using Durbin's formulation, equation (2),

$$I_u = I_o A_o \int_o^m G(t)\,dt \tag{4}$$

Equations (1) through (4) describe only the excretion of the plutonium which reaches the circulatory system. Other models have been established to evaluate internal depositions of transportable plutonium, but all are related to these basic models.

LUNG MODEL

The respiratory system is the primary route of entry into the body for the majority of accidental intakes of plutonium. The fraction of the inspired plutonium that will ultimately reach the circulatory system is dependent on many factors that affect the deposition, retention, distribution, and absorption in the lung. Particle size and density, chemical form and solubility, specific activity and respiratory rate are some of the more important factors involved in these physiological and biochemical processes. The Task Group Lung Model may be used to estimate many of these factors (TC66). Translocation of plutonium from the lung to other tissue (bone, liver) with half-times of 50 to 500 days will significantly influence the urinary excretion rate for extended periods. For inhalation cases, Langham's urinary excretion model, equation (1), may not provide a valid prediction of excretion rates, thus cannot be used to estimate systemic burdens under model conditions.

Healy developed a lung model that may be used to predict the urinary excretion rate if the amount of plutonium in the lung and the effective retention half-time is known (He57). His model assumes that equation (1) describes the excretion rate of each increment entering the blood and that the sum of the excretion rates of each increment gives the total excretion. On this basis, he derived an expression to estimate human urinary excretion over an extended period after an inhalation incident.

$$E_u(t) = A\lambda_s I_L \int_o^t e^{-\lambda x}(t + 1 - x)^{-0.74}dx \qquad (5)$$

Where E_u, A, and t have the same meanings as equation (1), λ_s is the rate of transfer from the lung to blood which is assumed to be equal to (λ) the overall lung elimination rate, I_L is the apparent initial quantity of plutonium retained in the lung after the rapid clearance to the gastrointestinal tract during the first week, x is the time since absorption into the blood.

Urinary excretion rates predicted by equations (1), (2), and (5) are compared in figure 1 (La64). The primary difficulty with practical application of the lung exposure model is associated with the limited data normally available for selecting valid values for λ and λ_s. However, for inhalation exposures, estimates obtained with this model appear to be far more realistic than those obtained with the basic systemic model.

Chelation therapy influences the urinary excretion rate of plutonium, and these models cannot be used to obtain a valid prediction of the urinary excretion rates after chelation treatments.

Pu-DTPA EXCRETION MODEL

Some simplification would be necessary in the formulation of a model to describe the very complex physiological processes of retention, translocation, and excretion of plutonium even if adequate experimental data are available. The administration of a chelating agent adds other parameters. Prior to discussing the derivation of the proposed Pu-DTPA excretion model, the biochemistry of plutonium is reviewed with respect to the physiological mechanisms of retention and excretion to include interactions with a chelating agent such as DTPA.

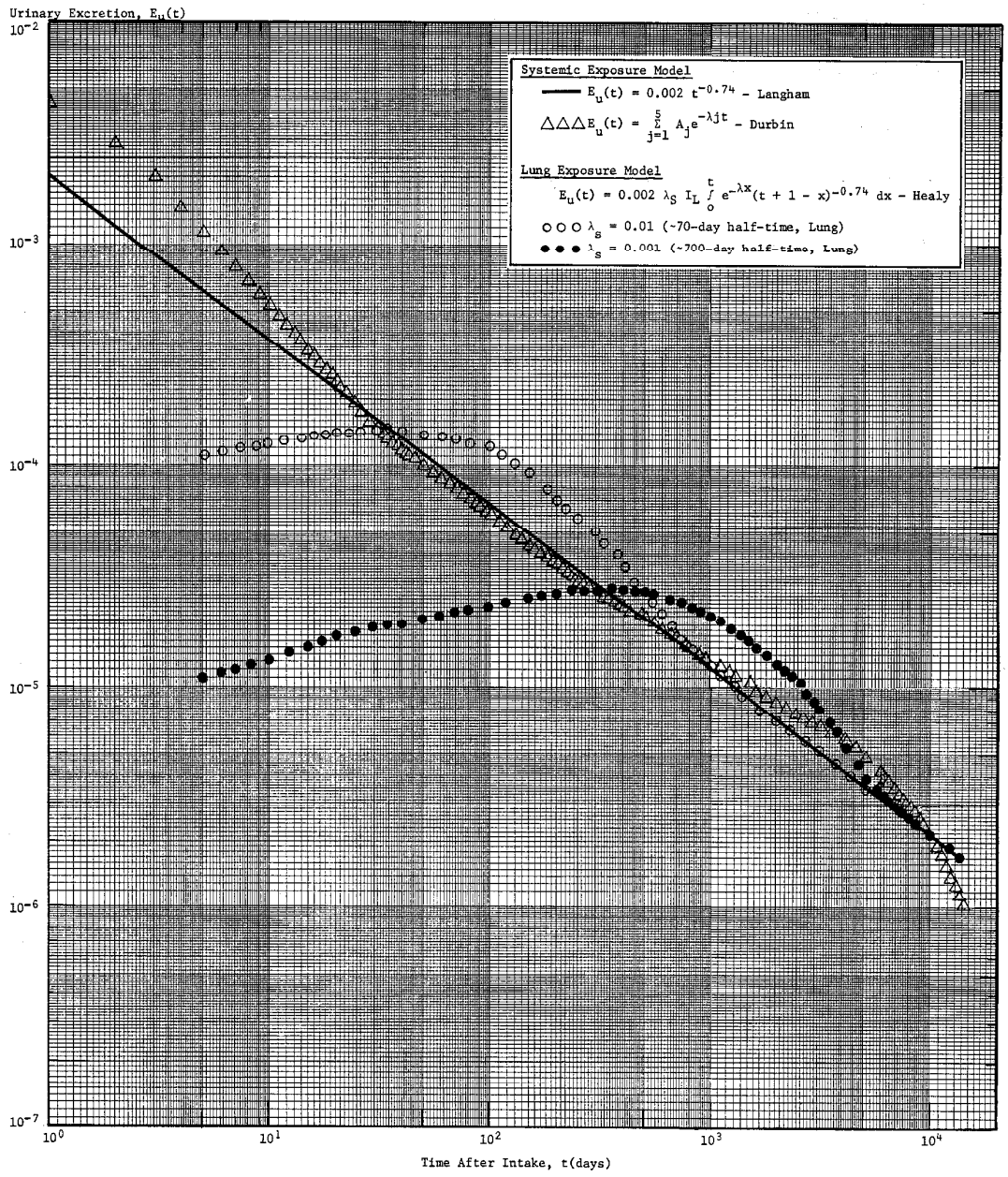

FIGURE 1. FRACTIONAL URINARY EXCRETION AS A FUNCTION OF TIME AFTER AN ACUTE PLUTONIUM EXPOSURE

This paper reviews briefly the chemistry of plutonium under physiological conditions, shows how systemic plutonium is translocated and metabolized in the body, discusses some reactions and interactions involved in the formation of the plutonium chelate, describes important excretion mechanisms for chelated plutonium, outlines the physiological basis for the Pu-DTPA excretion models, and explains the derivation of the mathematical models for single and multiple DTPA treatments.

PLUTONIUM CHEMISTRY UNDER PHYSIOLOGICAL CONDITIONS

In aqueous plutonium solutions all four valency states can coexist in equilibrium. Plutonium cations tend to hydrolyze, form polymers or particulates, and interact with complexing anions under physiological conditions. Hydrolytic reactions may be modified by the mass of plutonium or the presence of complexing anions.

In the human body, at about pH 7 uncomplexed plutonium ions are not likely to exist to any significant extent. The tendency of plutonium to hydrolyze in the gastrointestinal tract to form relatively insoluble compounds accounts for the extremely low systemic absorption. Chelation with DTPA will probably increase the fraction absorbed from $\sim 10^{-5}$ to $\sim 10^{-2}$ (Ba72). Plutonium forms stable complexes with the serum protein transferrin. Pu(VI) and Pu(IV) transferrin complexes have the greatest stability.

PLUTONIUM METABOLISM

For systemic plutonium the most important metabolic routes are shown in figure 2. It has been suggested that plutonium may be transported from the site of entry (lung or wound) to the bloodstream as a freely diffusible complex with some of the low molecular weight components of the tissues or body

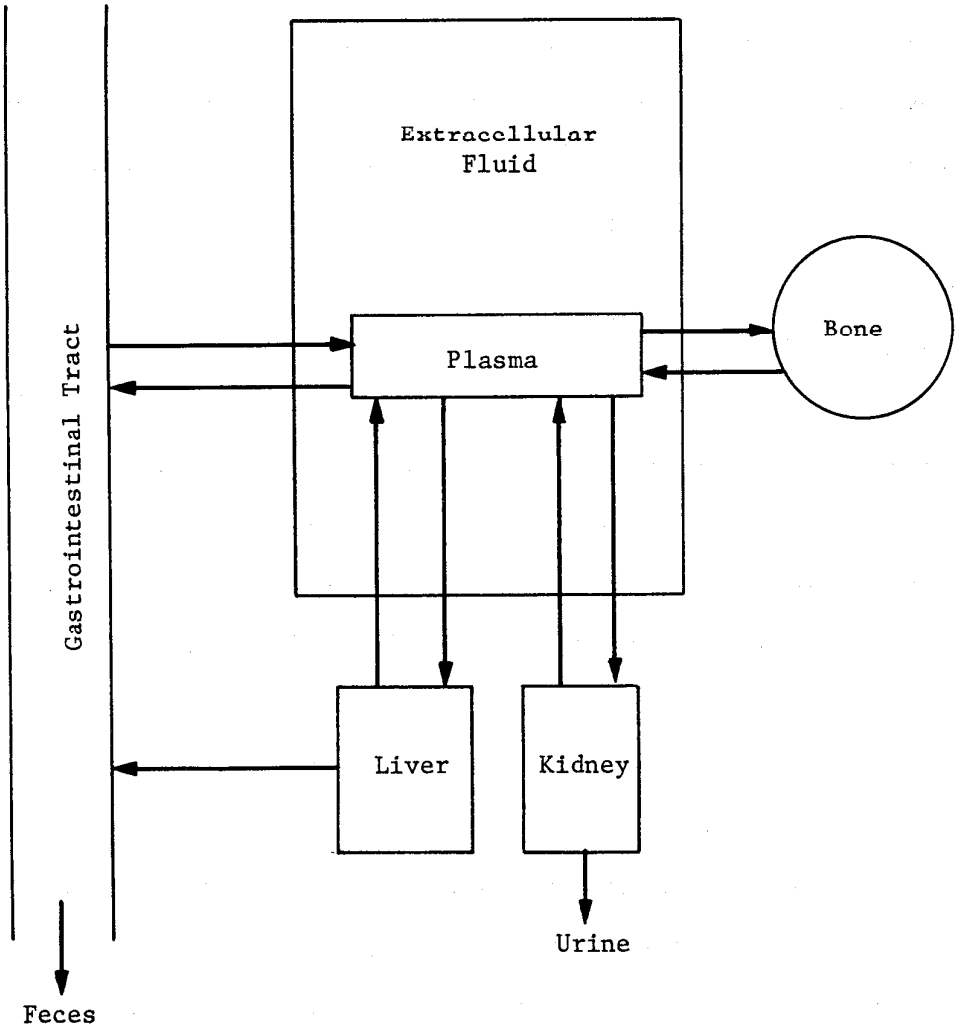

FIGURE 2. PRINCIPLE METABOLIC PATHWAYS OF TRANSPORTABLE PLUTONIUM IN THE BODY

fluids (Tu68). In blood, greater than 90% of the plutonium becomes bound to transferrin, the plasma protein that binds iron (Bo65). The remainder is divided between other macromolecules and low molecular weight substances like sugar or amino acids. Transfer of plutonium from the transferrin of the blood to bone or the tissues of other organs may also involve some type of diffusible complex.

Large collodial plutonium particles are rapidly removed from the blood by the liver. Data for man and other mammals show that the removal of monomeric plutonium from the blood by the kidney is a slow process (Va73). From the plasma clearance rates and the urinary excretion rates derived by Durbin (Du72) for an adult human being in reasonably good health, it can be calculated that the kidneys clear only 3 to 4% of the plasma plutonium in 24 hours.

The metabolic behavior of plutonium in man is probably not unlike its behavior in smaller mammals even though significant species differences have been reported (Va73). In small mammals, plutonium reaching the bloodstream is initially deposited primarily in bone and liver. Subsequent translocation between soft tissue and bone is an important mechanism of in vivo plutonium behavior. As plutonium is cleared from the plasma, loosely bound deposits in tissue are mobilized by the shifting equilibria with extracellular fluids. In the skeleton, plutonium is retained for long periods (retention half-time of 100 to 200 years). It may be mobilized in the normal course of bone remodeling, but a major fraction of it is redeposited or translocated to the liver. Plutonium deposited in the liver is also slowly transformed to an immobile form. As time passes, progressively larger amounts of plutonium in the skeleton and liver are withdrawn from equilibria with extracellular fluids. Thus the daily amount of plutonium excreted in urine becomes smaller

with time due to its immobilization in tissue, even though a constant fraction is cleared from plasma each day. Without therapy, the total amount excreted does not reduce the urinary excretion rate since the body burden is not reduced appreciably by normal elimination processes.

EFFECT OF CHELATING AGENT

A significant fraction of the systemic plutonium may be removed from the body by administering a metabolically stable chelate before it is immobilized in bone or liver tissue. Schubert presented a simplified method for estimating the degree to which a chelating agent binds in vivo (Sc72). The fraction chelated can be characterized to a first approximation by simple mass action,

$$M + L = ML$$

where M and L are the plutonium and the chelating agent and ML is the soluble chelate. Thus the fraction of M present as ML is

$$\frac{[ML]}{[M]} = k[L]$$

where k is the equilibrium or formation constant for the reaction. In the body, this constant must be considered with side-reaction coefficients of other interfering ions such as Ca^{++}, OH^{-}, H^{+}, etc.; however, if one predominates, the others can be ignored. The fraction chelated will approach a constant value or even 100%, depending on the relative reaction times and concentration of the agent in extracellular fluid.

DTPA EXCRETION

Analytical data on DTPA concentration in a worker's urinary voids, collected after one gram of the chelate was administered intravenously, show that approximately 99% of it is excreted in urine with a half-time of about 2 hours (Jo72), which agrees with the data observed for ^{90}Y-DTPA or ^{140}La-DTPA

in man (Kr57). Following aerosol chelation, a similar half-time was observed when the DTPA reached its maximum concentration in urine 4 to 5 hours after administration. The maximum concentrations observed in urine were $\sim 10^{-2}$ M and $\sim 10^{-3}$ M for DTPA administered intravenously and as an aerosol, respectively; however, the apparent difference in concentrations of DTPA in plasma is not significant since the chelate can compete effectively with the interfering ions in plasma and other extracellular fluid at very low concentration levels ($\sim 10^{-6}$).

At pH 7, DTPA and other metabolically stable chelates with a low charge can diffuse into intracellular fluids. The penetration of DTPA and its heavy metal chelates into the intracellular spaces of the body is an important mechanism that controls the excretion of chelated plutonium in urine or feces.

After a single treatment with DTPA, urinary excretion of the deposited plutonium rises sharply and then decreases rapidly. The daily excretion rate of plutonium is elevated approximately 80 times above normal levels. The chelated plutonium is eliminated with half-times of $\sim$12 hours and $\sim$7 days. About one-fourth of the plutonium excreted is associated with the more rapid elimination rate.

On the basis that 99% of the DTPA in plasma is excreted in urine with a half-time of 2 hours, it is estimated that the remaining 1% diffuses into extracellular fluid with an effective half-time of $\sim$7 days. After about 21 hours, the DTPA concentration in plasma and other extracellular fluids will reach the same level ($\sim 10^{-6}$ M) but the concentration in plasma will continue to decrease due to the rapid renal clearance rate.

The fraction of available systemic plutonium complexed with DTPA in the form of a diffusible chelate is roughly constant. The empirical power

function variable for urinary excretion, equation (1), can be used to estimate the fraction of deposited plutonium available for chelation if unity is assumed at the time of intake, $(t_o + 1)^{-0.74}$. The total amount of plutonium eliminated in urine will be reduced proportionally if the treatment is delayed.

As plutonium in the plasma and the extracellular fluid is complexed with DTPA, mobilization of loosely bound plutonium from tissue will be accelerated. This process of shifting equilibria continues until the DTPA concentration is reduced to a level where transferrin protein or other interfering ions predominate in binding plutonium.

Urinary excretion of chelated plutonium is controlled by rapid renal clearance from the plasma (2-hour half-time) and diffusion from extracellular fluid into the plasma (∿7-day half-time). One plausible hypothesis is that the renal clearance of DTPA from plasma (2-hour half-time) and the diffusion rate of DTPA between plasma and other extracellular fluids (∿7-day half-time) are responsible for the two observed exponential urinary excretion rates with half-time of 12 hours and 7 days, respectively. The obvious difference in the 2-hour DTPA renal clearance rate and the 12-hour urinary excretion rate for chelated plutonium may be due to the relatively slow rate of decorporation from transferrin. Constant decorporation and chelation at the slower rate while DTPA concentrations in plasma exceeds 10^{-6} M appears to be a logical explanation.

DERIVATION OF SINGLE-TREATMENT MODEL

An empirical equation analogous to equation (2) has been derived to predict the excretion rate after a single chelation,

$$E_u(t) = I_a A_o G(t) + \Delta E(t - t_c) \tag{6}$$

where $t \geq t_c$ and $\Delta E(t - t_c)$ represents the transient increase in excretion rate due to chelation, and the first term represents long-term behavior observed after the transient has passed.

Empirically,

$$\Delta E(t - t_c) = I_o G(t_c)[A_6 e^{-\lambda_6 (t-t_c)} + A_7 e^{-\lambda_7 (t-t_c)}] \tag{7}$$

where t_c is the time after intake at which chelation is administered, $A_6 = 0.2$, $A_7 = 0.044$, $\lambda_6 = 1.3 d^{-1}$ and $\lambda_7 = 0.1 d^{-1}$ are empirical constants, and I_o and $G(t_c)$ have the same meanings as equation (2).

The first term of equation (6) is the same as equation (2), except that the actual initial intake, I_o, has been replaced by an apparent intake, I_a I_a is less than I_o by the total amount removed by chelation (R),

$$I_a = I_o - R \tag{8}$$

where

$$R = \int_{t_c}^{\infty} \Delta E(t - t_c)dt = I_o G(t_c)\left(\frac{A_6}{\lambda_6} + \frac{A_7}{\lambda_7}\right) = 0.59\ I_o G(t_c) \tag{9}$$

Equation (9) shows that a single chelation can effect removal of 59% of the transportable intake. If chelation is administered immediately after intake ($t_c = 0$), 59% of the initial intake is removed. If chelation is delayed, the quantity removed is reduced in proportion to the relative excretion rate, G(t). Excretion rates predicted by these equations for a single DTPA treatment, administered immediately and 2 days after a plutonium uptake, are compared with Langham's excretion model in figure 3.

Equation (9) suggests an alternative expression for $\Delta E(t - t_c)$ that will prove convenient later, viz.,

$$\Delta E(t - t_c) = Rf(t - t_c) \tag{10}$$

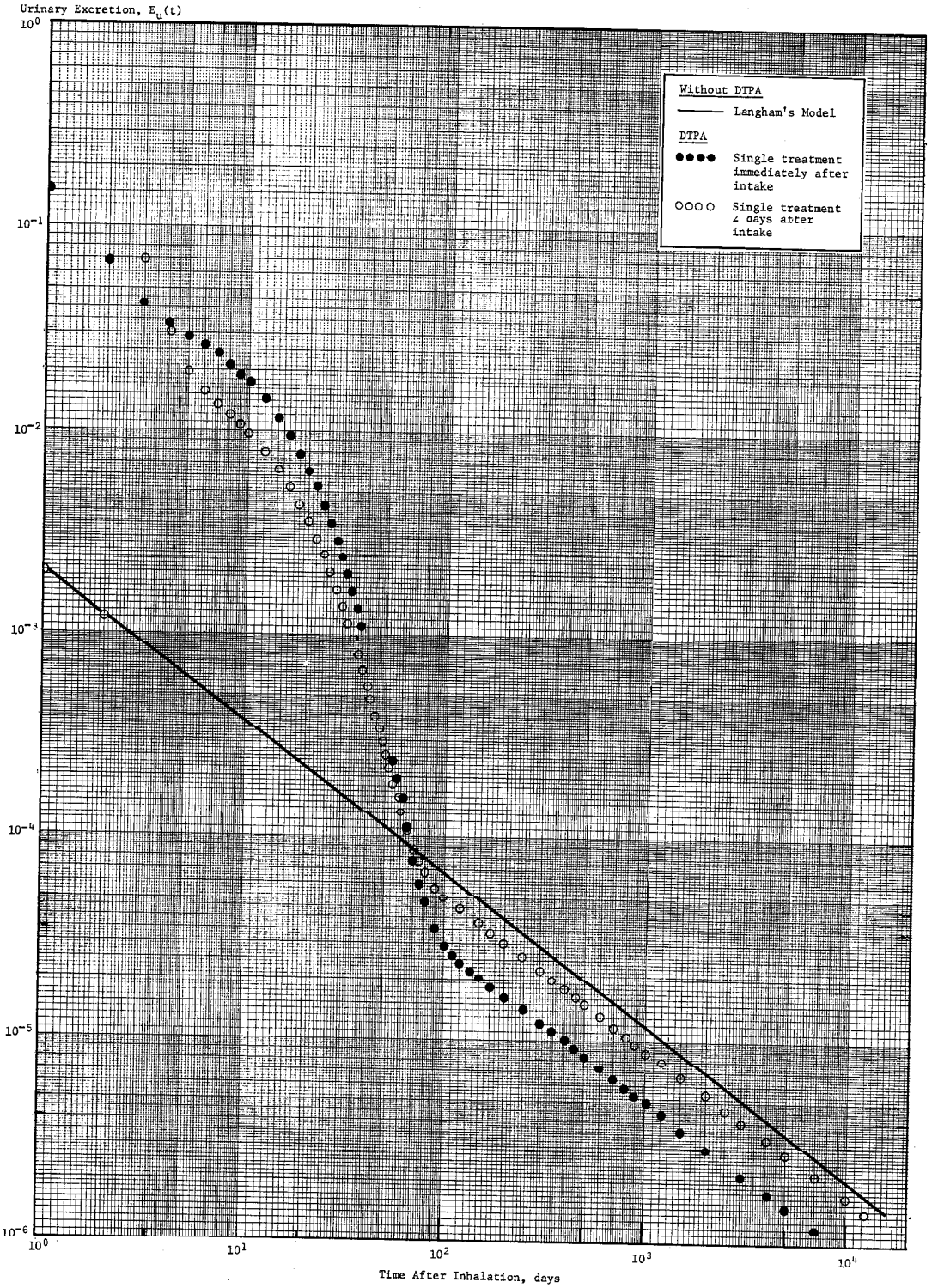

FIGURE 3. COMPARISON OF PREDICTED URINARY EXCRETION RATES AFTER ACUTE INTAKE OF TRANSPORTABLE PLUTONIUM WITH DTPA ADMINISTERED IMMEDIATELY AND TWO DAYS AFTER CONTAMINATION INCIDENT

where, from equations (7) and (9),

$$f(t - t_c) = \left[A_6 e^{-\lambda_6(t-t_c)} + A_7 e^{-\lambda_7(t-t_c)}\right] \Big/ \left(\frac{A_6}{\lambda_6} + \frac{A_7}{\lambda_7}\right) \qquad (11)$$

The convenience of this formulation is that R represents the total amount removed by chelation and the fraction of that amount removed at any time, t, is given by $\int_{t_c}^{t} f(x - t_c)dx$.

MULTIPLE TREATMENTS

The fraction of systemic plutonium removed from the body by DTPA therapy can be increased with multiple chelation. The rate of excretion may also be predicted by an empirical formula. To derive such a formula, there are two principal empirical observations that must be made. The first is that the combined effects of multiple chelations may be expressed as the sum of effects of individual chelations, as though they were independent. Thus, the general equation for n chelations, analogous to equation (6), is

$$E_u(t) = I_a(t)A_o G(t) + \sum_{j=1}^{n} \Delta E_j(t - t_j) \qquad (12)$$

In this expression, each of the $\Delta E_j(t - t_j)$ is given by equation (10), with an appropriate index attached,

$$\Delta E_j(t - t_j) = R_j f(t - t_j) \qquad (13)$$

and $f(t - t_j)$ is the same function defined by equation (11). The total amount removed by a given chelation, R_j, is a slightly more complex function than that for a single chelation, equation (9), and will be discussed later. The apparent intake, $I_a(t)$, is less than the actual initial intake, I_o, by the cumulative amounts removed by chelation.

$$I_a(t) = I_o - \sum_{j-1}^{n} R_j \tag{14}$$

$I_a(t)$ is written as a function of time because successive chelations are administered at different times. Thus, even though I_o and each of the R_j are constants, $I_a(t)$ changes each time another chelation is administered.

The second of the two principal empirical observations relates how the effect of the latest chelation is influenced by prior chelations. The key points are that (1) plutonium bound to DTPA from prior chelations is not available to subsequent chelations, and (2) each chelation binds as much plutonium as possible by DTPA at that time.

Point (1) is embodied in the observation that the total amount to be removed by a given chelation, R_j, is proportional to the apparent intake at the time of chelation.

$$R_j \alpha I_a(t_j) = I_o - \sum_{K=1}^{j-1} R_K \tag{15}$$

Point (2) may be restated by saying that no unbound plutonium is available for complexing with DTPA immediately after chelation. But unbound plutonium does become available gradually, since the observed excretion rate reverts to $I_a(t)A_oG(t)$ after the chelation transient has passed. It has been observed that the fraction of this unbound plutonium available at some time, t, after chelation at time, t_j, is the same as the fraction of R_j removed at that time, namely,

$$\int_{t_j}^{t} f(x - t_j)dx$$

This last observation provides enough information to explain the empirical equation for the total amount removed by a given chelation.

$$R_j = 0.59\ I_a(t_j)G(t_j) \int_{t_j-1}^{t_j} f(x - t_{j-1})dx \qquad (16)$$

Equations (11) through (14) and (16) provide the means of predicting excretion rates under conditions of multiple chelations. They are repeated below to provide a more compact description.

$$E_u(t) = I_a(t)A_oG(t) + \sum_{j=1}^{n} \Delta E_j(t - t_j)$$

$$I_a(t) = I_o - \sum_{j=1}^{n} R_j, \text{ where } t \geq t_c$$

$$\Delta E_j(t - t_j) = R_j f(t - t_j)$$

$$R_j = \left(\frac{A_6}{\lambda_6} + \frac{A_7}{\lambda_7}\right) I_a(t_j)G(t_j) \int_{t_{j-1}}^{t_j} f(x - t_j - 1)dx$$

$$f(t - t_j) = \left[A_6e^{-\lambda_6(t-t_j)} + A_7e^{-\lambda_7(t-t_j)}\right] \left(\frac{A_6}{\lambda_6} + \frac{A_7}{\lambda_7}\right)$$

$$A_6 = 0.2,\ A_7 = 0.044,\ \lambda_6 = 1.3d^{-1},\ \lambda_7 = 0.1d^{-1}.$$

DETERMINATION OF CONSTANTS

The empirical constants for equation (7), A_6, A_7, λ_6, and λ_7 were determined using the mathematical expression derived to describe urinary excretion of transportable plutonium after DTPA therapy (Jo72).

$$E_u(t_c) = 1.3e^{-1.3(t-t_c)} + 0.28e^{-0.1(t-t_c)} + E_u(t) \qquad (17)$$

where $E_u(t_c)$ is the average rate of urinary excretion at time, $t - t_c$, expressed as a fraction of the amount excreted during the first day after treatment, t is the time elapsed since the intake, t_c is the time at which chelation occurs and $E_u(t)$ is the fraction that would have been excreted without therapy. The constants, 1.3 days $^{-1}$ (λ_6) and 0.1 days $^{-1}$(λ_7) describe the characteristic excretion pattern with half-times of $\sim$12 hours and $\sim$7 days

observed after DTPA therapy. Even though this equation was derived from excretion rates, observed for 24-hour intervals, urinalysis data for individual voids collected during the first day after DTPA treatments show that the expression is valid for smaller time increments.

The constants A_6 and A_7 can be calculated using equation (17) and the increase in urinary excretion observed for workers the first day after treatment. Parker reported that a single treatment multiplies by 30 to 100 the urinary excretion the first day after DTPA therapy (Pa73). At Savannah River Plant enhancement ratios of 70 to 80 have been observed for workers with well-defined systemic plutonium burdens based on Langham's urinary excretion model. Using an average enhancement ratio of 78, the values for A_6 and A_7 are 0.20 and 0.044, respectively, and values for λ_6 and λ_7 are 1.3 and 0.1, respectively.

DTPA AEROSOL[1]

There are advantages of DTPA therapy by aerosol inhalation compared with administration by intravenous injections immediately after a plutonium inhalation incident. The most important advantage is that a larger fraction of the transportable plutonium initially deposited in lung can be removed from the body by aerosol chelation. Only about 60% of the plutonium that becomes bound to transferrin in plasma can be removed from the body by the initial DTPA treatment. If plutonium is chelated by mass action in the lung

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[1] DTPA was administered as an aerosol on the basis of verbal consent. Until a written Investigational New Drug (IND) permit is obtained to authorize aerosol administration, chelation therapy will be limited to the intravenous injection procedure prescribed by the existing IND.

prior to reaching the bloodstream, approximately 99% of the Pu-DTPA is excreted in urine with a half-time of ~2 hours. Once plutonium has been incorporated in plasma, no significant difference in the effectiveness of DTPA therapy occurs, whether administered intravenously or as an aerosol. Aerosol chelation also has the advantage of being more readily accepted by workers since it is a nonsurgical procedure.

APPLICATION OF THE Pu-DTPA MODEL

Equations for the Pu-DTPA model are presented as a means of predicting the rate of plutonium urinary excretion in the presence of a chelate, their more practical application is just the converse; given excretion data, initial and apparent intakes may be determined. A recent plutonium inhalation incident was selected to demonstrate use of the model for early assessment of a worker's systemic burden from urinary excretion data during extended DTPA therapy. Six workers were exposed to airborne plutonium contamination inadvertently released during the repair of refrigeration equipment used to cool $^{238}PuO_2$ in a production facility. $CaNa_3$-DTPA was administered by aerosol to five of these workers immediately following the inhalation incident. They were given additional chelation treatments at later times. A set treatment schedule was not followed. The proposed model was not available at the time of the incident. Hepatic disease in the sixth man precluded the use of DTPA.

The workers were all exposed to airborne activity levels to 1.2×10^{-7} μCi ^{238}Pu/cc for up to 10 minutes. A summary of each man's early bioassay-exposure data is shown in table 1. Nasal activity is the total for both nares. Activity in dehydrated feces was determined by direct counting with a phoswich detector.

Plutonium urinary excretion data for the six workers are compared in figures 4 through 9 with the predicted excretion curves based on the Pu-DTPA and Langham's urinary excretion models. The excretion curves for the various treatment regimens predicted by the empirical equations fit the bioassay data obtained for these cases reasonably well. These data show how the model can be used to evaluate a worker's bioassay data. Estimated intake, therapy, and body burden data for each worker are summarized in table 2.

Pretreatment and posttreatment chest x-rays, complete blood count, and urinanalysis on the five treated individuals were normal. SMA-18 chemical profile done 20 months past exposure, also was normal for each of the treated individuals.

OPTIMAL DTPA DOSAGE SCHEDULE

An optimum dosage schedule is suggested by the fact that one term in the Pu-DTPA model, $G(t_j)$, decreases with time while another term, $\int f(x - t_{j-1})$, increases with time. Any regimen for DTPA therapy must be initiated as soon as possible after a contamination incident if it is to be most effective. The first chelation removes much more than any subsequent chelation because the amount removed is proportional to $I_a(t_j)$ and $G(t_j)$. Thus, the timing of the initial treatment is most important especially in cases where extended therapy is indicated.

A computer code was written to evaluate equations (3), (4), and (16) for a series of postulated conditions and the optimum schedule for a series of five DTPA treatments was determined by inspection of the data. The percentage of transportable plutonium that would be excreted in urine during the first 10 weeks after an inhalation incident are listed in table 3.

TABLE 1
SUMMARY OF EARLY BIOASSAY-EXPOSURE DATA

Bioassay-Exposure Data	Employee A	B	C	D	E	F
Nasal smears, d/m ^{238}Pu	1270	920	120	200	4530	120
Fecal activity in 1st week, nCi ^{238}Pu[a]	5.2	0.9	0.2	2.4	2.1	4.9
In vivo count, nCi ^{238}Pu	<14	<6	<14	<16	<10	<7
Systemic burden from previous uptakes, μCi Pu	0.004	0	0	0.002	0.001	0.005

[a] Cathartic phospho-soda administered within 2 hours of incident.

TABLE 2
SUMMARY OF BIOASSAY DATA EVALUATION

Uptake-Therapy Data	Employee A	B	C	D	E	F
Activity initially deposited in lungs, nCi Pu	∿12	∿3	∿0.6	∿11	∿8	∿12
Initial systemic burden, nCi Pu	4.7	1.8	0.27	6.4	4.5	6.1
DTPA treatments	13	10	7	14	13	0
Activity chelated in lungs, nCi Pu	∿0.7	-	∿0.1	∿1.0	-	0
Systemic burden removed by therapy, %	71.8	70.5	68.2	72.3	70.1	0
Residual systemic burden, nCi Pu	1.2	0.5	0.1	1.7	1.3	6.0

TABLE 3
EFFECTS OF CHELATION — DTPA AEROSOL

PERCENTAGE OF INHALED PLUTONIUM (TRANSPORTABLE) EXCRETED IN URINE

Week	No Treatment	Single Treatment[a]	Five Treatments[b]
1	0.642	37.94	42.17
2	.243	11.10	13.46
3	.166	5.525	7.696
4	.130	2.765	3.613
5	.108	1.391	1.805
6	.093	0.707	0.909
7	.083	.366	.462
8	.074	.195	.240
9	.068	.110	.128
10	0.062	0.066	0.072
Total →	1.669	60.016	70.056

[a] DTPA therapy on day 1 immediately after inhalation.
[b] DTPA therapy using optimal dosage schedule with treatments on day 1, day 2, day 4, day 7, and day 15.

SUMMARY

A large fraction of the readily available plutonium in extracellular fluids or loosely deposited in other tissues can be removed from the human body with DTPA therapy. To obtain maximum effectiveness, therapy must be initiated immediately after a contamination incident. The proposed Pu-DTPA urinary excretion model can be used to make early assessments of the systemic body burden and determinations of optimal treatment schedules.

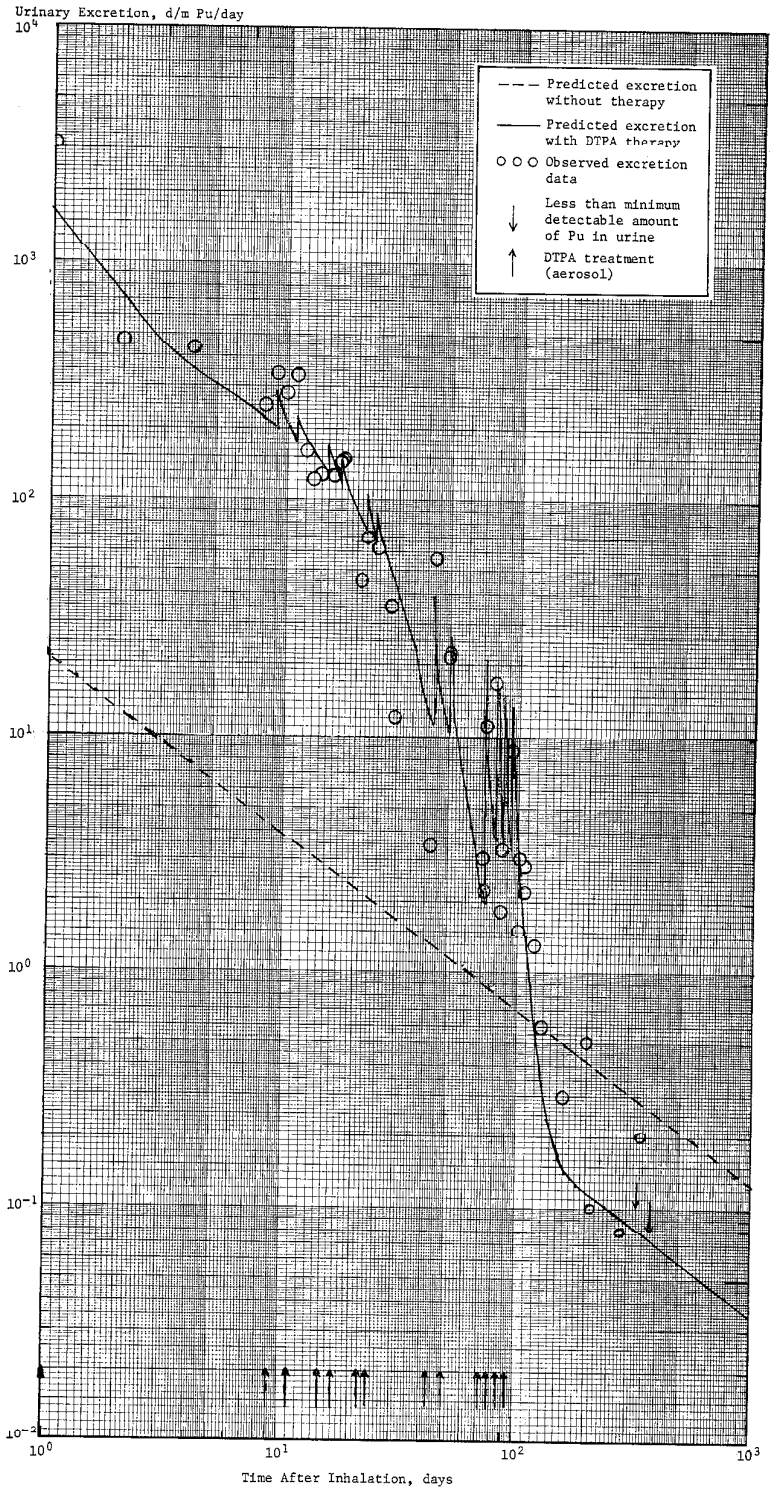

FIGURE 4. PREDICTED AND OBSERVED URINARY EXCRETION OF PLUTONIUM — CASE A

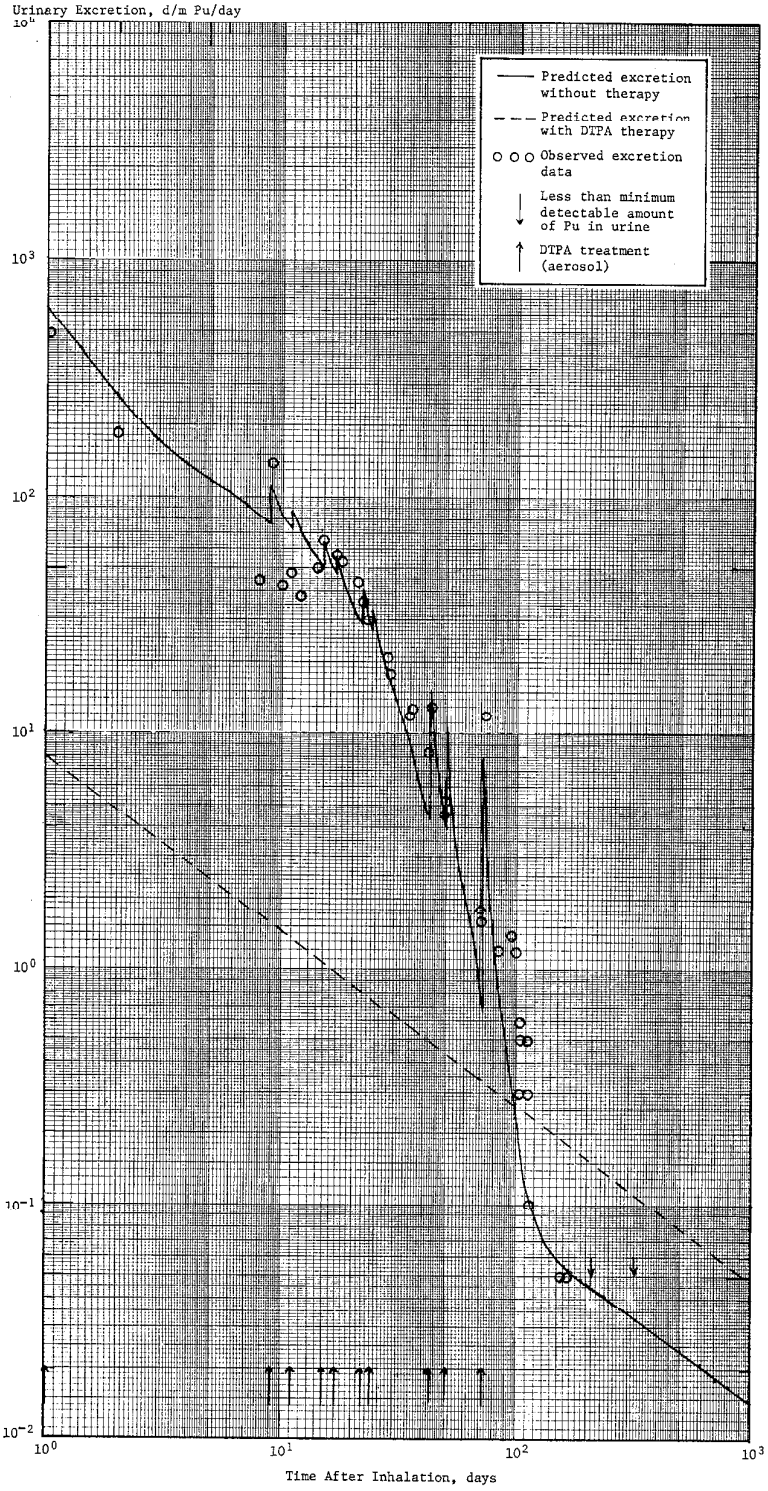

FIGURE 5. PREDICTED AND OBSERVED URINARY EXCRETION OF PLUTONIUM — CASE B

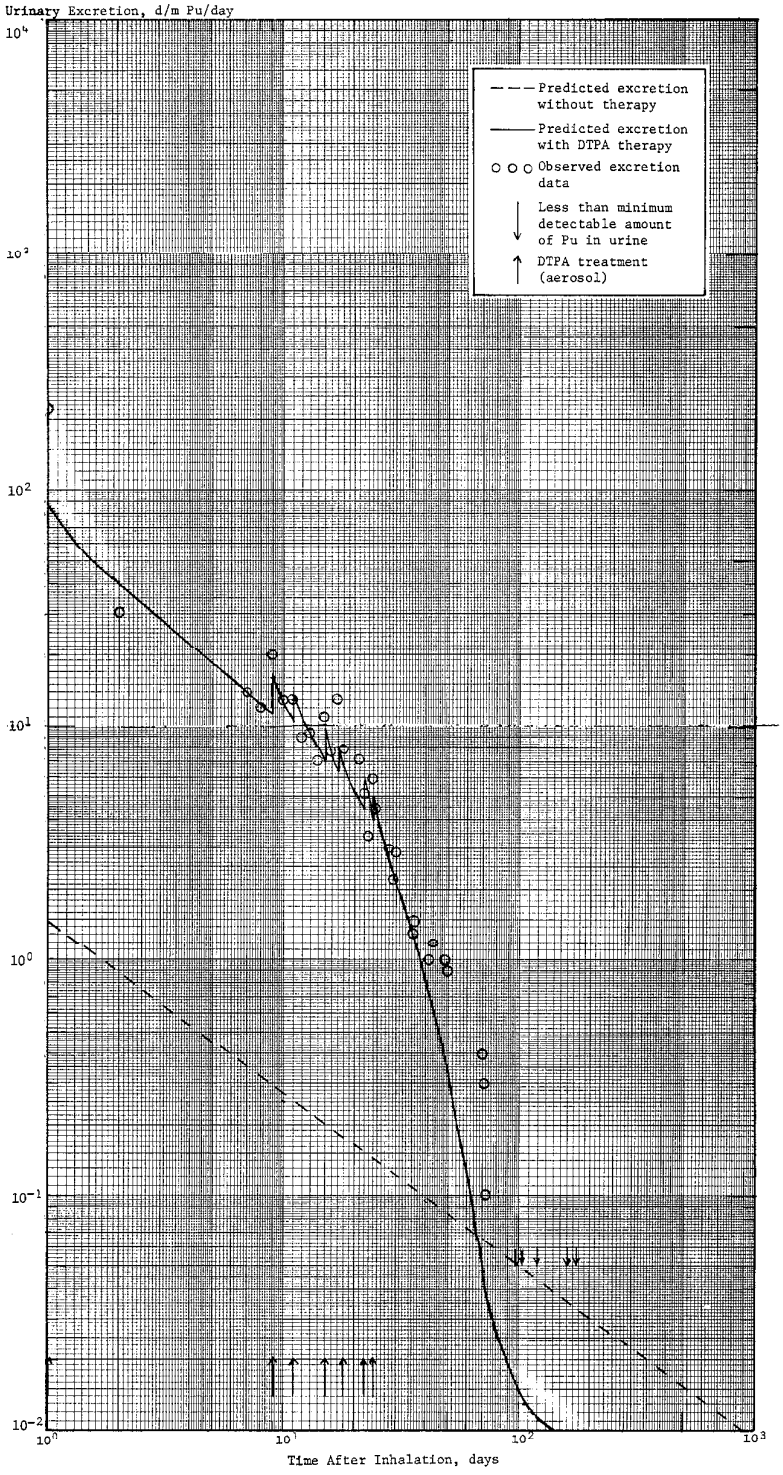

FIGURE 6. PREDICTED AND OBSERVED URINARY EXCRETION OF PLUTONIUM — CASE C

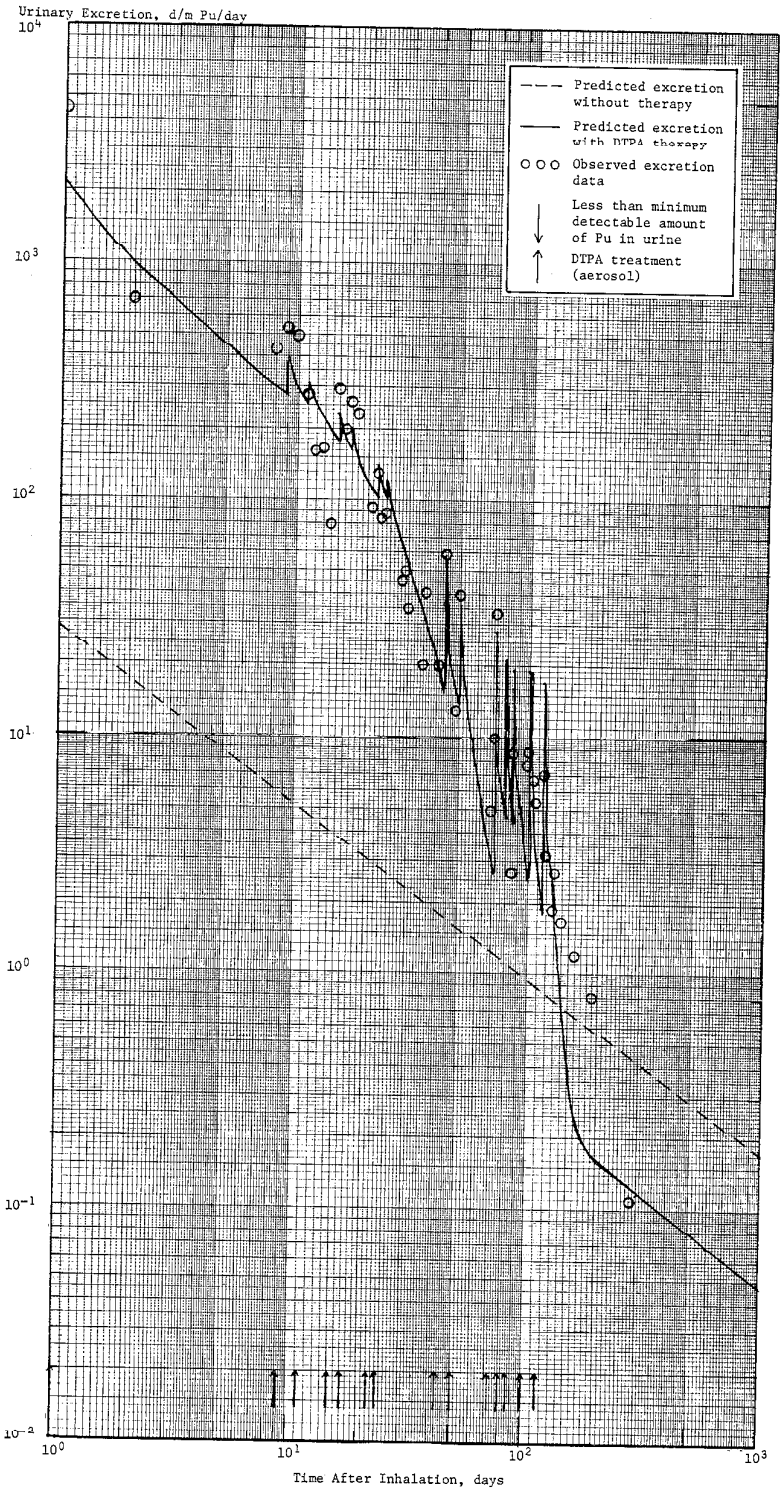

FIGURE 7. PREDICTED AND OBSERVED URINARY EXCRETION OF PLUTONIUM — CASE D

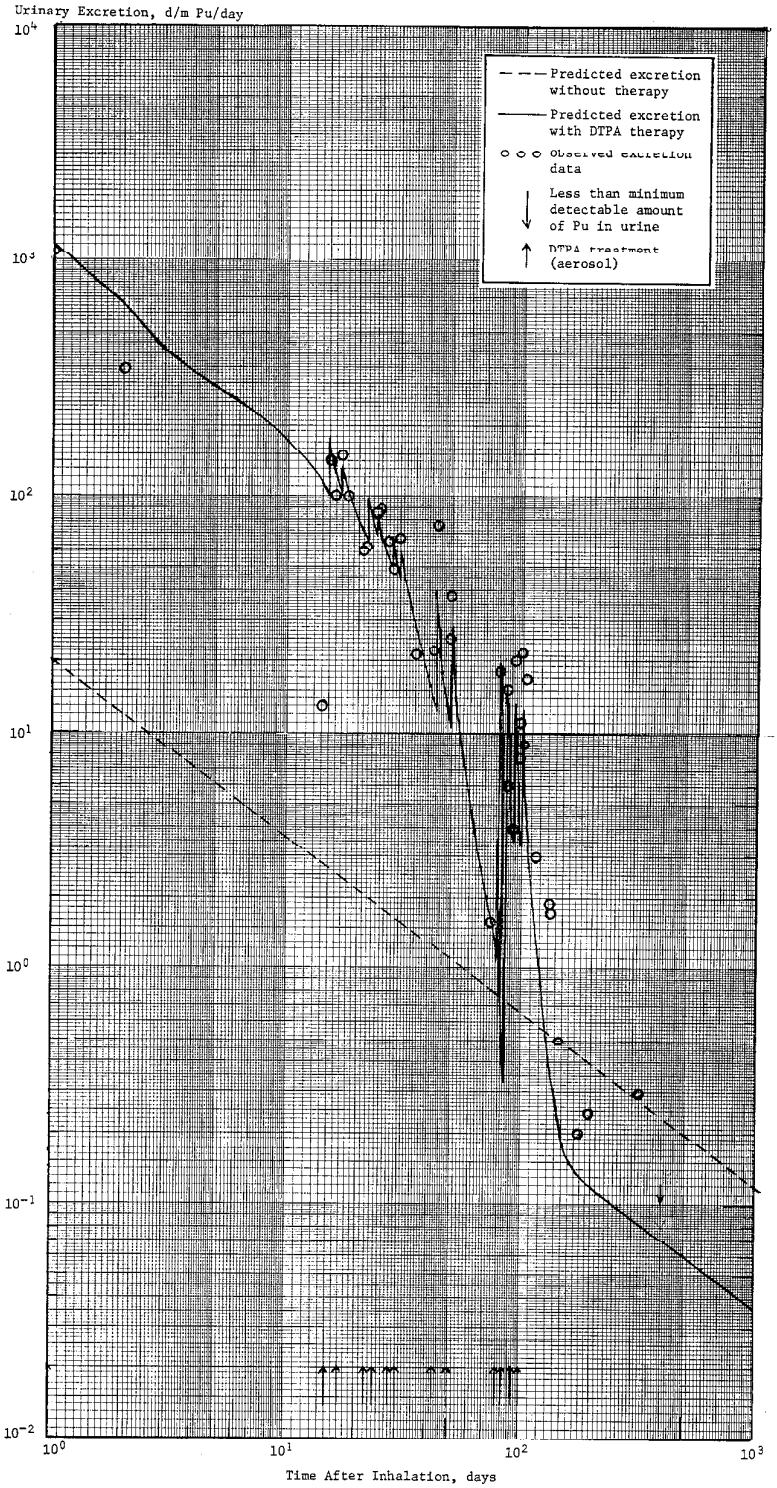

FIGURE 8. PREDICTED AND OBSERVED URINARY EXCRETION OF PLUTONIUM — CASE E

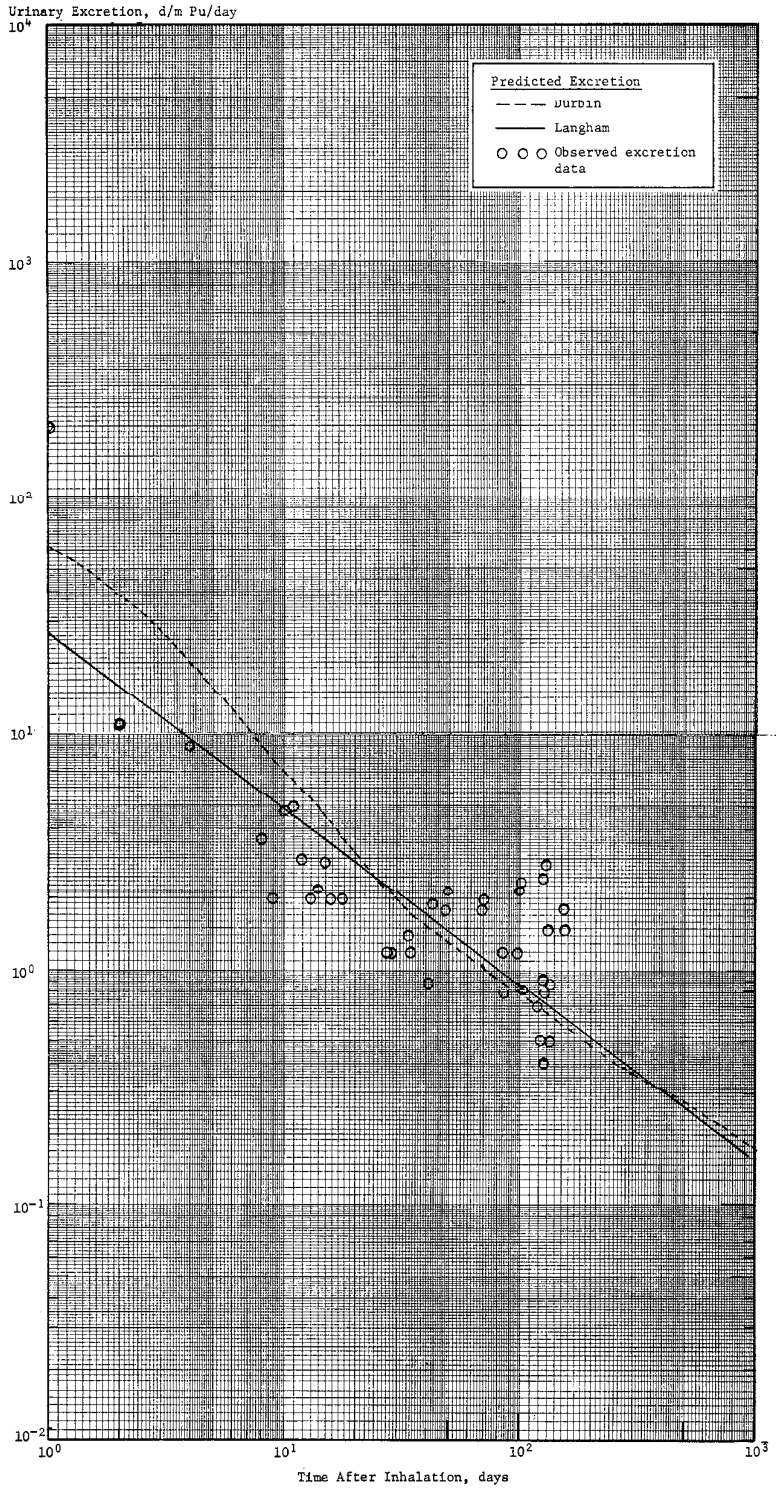

FIGURE 9. PREDICTED AND OBSERVED URINARY EXCRETION OF PLUTONIUM — CASE F

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